A CLINICAL STUDY OF NEUROLOGICAL MANIFESTATIONS IN HIV

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CERTIFICATE

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DECLARATION

I solemnly declare that this dissertation entitled "**A CLINICAL STUDY OF NEUROLOGICAL MANIFESTATIONS IN HIV"** was done by me at Madras Medical College and Govt. General Hospital during 2004-2007 under the guidance and supervision of **Prof. V. RAJI, M.D.** This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE (BRANCH - I).

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CONTENTS

INTRODUCTION

In the early 1980s as the systemic manifestation of the AIDS were first, described, investigators realized that human immunodeficiency virus type 1 infection could affect the nervous system at every level. With HIV infection increasing by the day in our society, neurological manifestations in HIV infection is not an uncommon occurrence. These neurological disorder occur either as a direct consequence of the HIV infection itself, or, as a immunological complication of the infection, or, as opportunistic infection of CNS, or, as a result of adverse reaction to antiviral agents.

Neurologic disease may manifest at any stage of the infection i.e. from the stage of Seroconversion to full fledged AIDS. In retrospective analysis it was observed that 10% of Patients with AIDS have neurological symptoms during the course of the illness, and 75% have evidence of CNS neuropathology at autopsy[1,2,3].

Neurological manifestations of HIV consists of CNS complications caused directly by HIV, and include cognitive disorders and other CNS disease such as myelopathy and the demyelinating neuropathies, and the secondary disorders caused by opportunistic infections, neoplasm, cerebrovascular events, as also the effects of metabolic derangements and medications.

Considering the protean manifestations of neurological illness in HIV infected, an analysis of neurological manifestations in this subset of Patients was made.

AIM OF THE STUDY

To study the pattern of neurological manifestations in HIV infected subjects.

To study the correlation of neurological manifestations with CD_4 count in these subjects.

REVIEW OF LITERATURE

Nervous system disease was not widely noted in the early years of HIV epidemic. However it is now recognized that almost every part of the nervous system can be affected not only by opportunistic infections but directly or indirectly by HIV itself.

Neurologic disease is the first manifestation of symptomatic HIV infection in roughly 10 to 20% of persons, while about 30 to 40% of patients with advanced HIV disease will have clinically evident neurologic dysfunction during the course of their illness[1,2]. The incidence of subclinical neurologic disease is even higher, autopsy studies of patients with advanced HIV disease have demonstrated pathologic abnormalities of the nervous system in around 75% of cases[2].

PATHOGENESIS

HIV crosses the blood brain barrier and enters the nervous system, early, probably concomitant with initial systemic infection[4]. The virus has been cultured from brain, nerve and cerebrospinal fluid from persons at all stages of HIV diseases including those without neurologic signs or symptoms[5]. Positive HIV – 1 cultures in CSF do not predict the presence or development of Neuro AIDS. It depends on a number of factors such as degree of immunosuppression and the molecular biology of the viral strain, particularly its neurovirulence.

HIV – 1 associated neural damage is most likely initiated by HIV – 1 infected and primed macrophages / microglia. The HIV – 1 infected macrophage appears to be hyperesponsive to activation stimuli. Both viral proteins and cellular products of HIV – 1 infected cells may act as neurotoxins. A complex interaction occurs between

HIV –1 infected macrophages / microglia and astrocytes that results in the release of proinflammatory cytokines TNF - α and IL – IB as well as PAF and arachidonic acid metabolites[6]. Ultimately, the cytokines upregulate HIV –1 infection in the brain. Although these products amplify neurotoxic and glial proliferatory effects of a small number of productively HIV – 1 infected cells, astrocytes produce TGF – B and macrophages release IL – 10, which independently downregulate proinflammatory cytokines. This may lead to chronic low – level inflammation, viral replication and tissue pathology.

Lastly, it appears that excitotoxic mechanism may underlie neuronal injury and death in HIV – 1 encephalitis[7]. This final common pathway could be the result of production or release of excessive amounts of glutamate, PAF or NMDA agonists such as quinolate[7].

PRIMARY HIV INFECTION OF THE BRAIN

HIV – 1 associated dementia complex

HIV – 1 associated dementia complex has been variously called AIDS dementia complex, AIDS encephalopathy. HIV encephalitis, and multinucleated giant cell encephalitis.

With uncommon exceptions dementia is a late complication of HIV disease, occurring in the setting of systemic symptoms and severe immunosuppression[8]. Cognitive impairment develops in about 30% of people with advanced AIDS and frank dementia in 15 to 20%, with an annual incidence after AIDS of approximately 7%[9]. There have been reports of dramatic decline in the frequency of HIV dementia after 1987, related to the earlier and more widespread use of antiretrovirals.

Though there is some variability among patients, the syndrome is sufficiently stereotypic to be relatively easily recognized, particularly in a patient who is well known to the observer. In adults, the clinical manifestation of HIV dementia suggests predominantly subcortical involvement, at least initially.

Typical symptoms include increasing forgetfulness, difficulty with concentration, loss of libido, apathy, inertia and waning interest in work and hobbies resulting in social withdrawal. Occasionally agitation or mania may be the initial manifestation. Generalized seizures can also occur as a manifestation of HIV dementia, however, they are usually not refractory and, in many cases, may be triggered by medications or illicit drugs.

Neurologic examination is often normal in the early stages of HIV dementia, although there may be demonstrable impairments of rapid eye and limb movements and diffuse hyperreflexia. As HIV dementia progresses, increased tone develops, particularly in the lower extremities and is usually associated with tremor, clonus, frontal release signs and hyperactive reflexes. Terminally, the patient is bed bound, incontinent, abulic or mute with decorticate posturing[10].

Price and Brew[10] have devised a staging system for HIV dementia that is widely used in both clinical and research areas. The scale combines functional impact of both cerebral and spinal cord dysfunction. This clinical staging system correlates well with performance on psychomotor speed measures and is useful to track progression and response to therapy. CT or MRI scans of the brain may be normal, but in setting of severe dementia the usual finding is diffuse atrophy and, on MRI, patchy or diffuse abnormal signal in the white matter on T2 - weighted images[11].

Severity Scales of Dementia

Stage	Dementia
0	Normal mental and motor function. Neurological signs are within the normal age - appropriate spectrum.
0.5	***Equivocal or subclinical:*** Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform ADL. Examination may be normal mildly abnormal; signs may include reflex changes (e.g. generalized increase in deep tendon reflexes with active jaw jerk, snout or glabellar sign) or midly slowed ocular movements, but without clear slowing of extremity movements or loss of their dexterity or strength.
1	***Mild:*** Able to perform all, but the more demanding aspects of work or ADL but with unequivocal evidence (symptoms or signs including performance on neuropsychologic testing) of intellectual or motor impairment. The abnormal motor signs usually include slow or clumsy movements or extremities.
2.	***Moderate:*** Able to perform basic activities of self care at home but cannot work or maintain more demanding aspects of daily life (e.g. maintain finances, read text more complex than a tabloid newspaper)
3	***Severe:*** Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output or motor liability.
4	***End Stage:*** Nearly vegetative. Intellectual and social comprehension and output are at a rudimentary level. Nearly or absolutely mute.

Aseptic meningitis

Bredesen et al[12] first reported 15 homosexual patients with aseptic meningitis. Levy et al[2] evaluated a total of 352 patients with AIDS and found two patients with aseptic meningitis.

In the setting of acute primary infection patients may experience a syndrome of headache, photophobia, and meningismus. Cranial nerve involvement may be seen, predominantly cranial nerve VII, but occasionally V and / VIII involvement. CSF findings include a lymphocytic pleocytosis, elevated protein level and normal glucose level. This syndrome, which cannot be clinically differentiated from other viral meningitis, usually resolves spontaneously within 2 to 4 weeks, however, in some patients it may become chronic[1,2,12].

Neuromuscular disorders

A wide range of peripheral nervous system disorders develop in patients with HIV infection, leading to pain, sensory symptoms, and muscle weakness. Both primary HIV - 1 associated nerve disorders and those secondary to opportunistic processes are well described. In addition, antiretroviral therapies such as ddI, ddC and d4T may cause or exacerbate peripheral neurophathies[13].

Four types of neuropathy are important to recognize, either because of their high prevalence or their therapeutic implications, or both. They are

1. Distal symmetric polyneuropathy (DSPN)
2. Mononeuropathy multiplex
3. Inflammatory demyelinating polyneuropathy
4. Progressive lumbosacral polyradiculopathy

Depending on the study population and the method of case ascertainment, clinical, electrophysiologic or pathologic evidence of peripheral neuropathy is present in about one - third to nearly 100% of patients with advanced HIV disease[14]. The incidence of neuropathy increases with declining CD4 cell count and advancing systemic HIV disease. Toxicity of the therapeutic drugs, notably dideoxyinosine (ddI), dideoxycytidine (ddC) and stavudine (d4T), is responsible for a increasing number of cases of neuropathy or for their progression.

Distal symmetric polyneuropathy

Distal symmetric polyneuropathy was initially described in patients with AIDS by Snider et al[1] and its clinical and pathological features have been further characterized by numerous investigators[15]. DSP may be diagnosed in >30% of patients with AIDS, after other recognized causes for polyneuropathy are excluded. DSP is usually associated with late stages of HIV disease, as indicated by the presence of opportunistic infections and significant wasting in the majority of patients with DSP[15].

The major presenting symptoms of DSP are numbness, distal paraesthesias and dysthesias, usually beginning in the lower extremities. A complaint of burning feet is reported by 23-100% of patients with AIDS evaluated for DSP in different series[15]. The upper extremities may be affected in a distal and symmetrical fashion later in the course of DSP. Muscle weakness is not a prominent symptom of DSP and generally occurs only late in the disease.

The most common signs of DSP in AIDS are depressed or absent reflexes at the ankles, relative to the knees[15]. The presence of hyperactive knee reflexes and depressed ankle reflexes may indicate concurrent myelopathy and neuropathy which is a common association in HIV infected individuals[16]. Vibratory thresholds are

increased, and pinprick and temperature are reduced in a stocking and glove distribution, whereas joint position sensation is relatively normal. Weakness is generally restricted to intrinsic foot muscles[15], unless DSP is very advanced, or other neurologic disorders are also present.

Several studies have demonstrated that mean sural nerve conduction velocity or amplitude is significantly reduced in HIV seropositive patients as compared with controls. Small or absent small nerve action potentials are the most common abnormalities in patients with DSP, although in occasional patients with DSP normal sural responses have been reported. Needle EMG may demonstrate signs of active or partial denervation with reinervation in distal leg muscles.

Mononeuropathy multiplex

In 1985, Lipkin et al[17] first described the occurrence of inflammatory neuropathy in 12 homosexual patient with lymphadenopathy syndrome, of whom nine presented with multiple, asymmetrical nerve involvement.

Patients with MM have asymmetric or proximal involvement of peripheral nerves and preservation of tendon reflexes in asymptomatic distributions. The typical neurologic presentation includes multifocal sensory and motor abnormalities in the distribution of cutaneous nerves, mixed nerves and nerve roots[17]. Cranial neuropathies are also a frequent feature of MM[17].

Although signs of focal or asymmetric multifocal axonal lesions are most typical in MM[13] electrodiagnostic abnormalities may be diffuse and symmetrical, similar to DSP or may indicate primary demyelination, with slowing of NCV and conduction block[17].

Inflammatory demyelinating polyneuropathy

Acute IDP (AIDP) and chronic IDP are most common in patients who are HIV seropositive and otherwise asymptomatic[18]. Several investigators have reported IDP upto one third of HIV infected patients referred for evaluation of peripheral neuropathy[18] whereas others have found a much lower incidence.

AIDP is characterized by rapidly progressive weakness in distal and proximal muscles of two or more limbs associated with generalized areflexia. Occasionally, bilateral facial weakness may be the presenting symptom. The clinical progression of AIDP is usually rapid and reaches its peak within the first 4 weeks of neurologic illness, with involvement of respiratory muscles in the most severe cases. CIDP is distinguished by a more slowly progressive clinical course that may be monophasic or relapsing over several months[18].

Electromyography typically shows signs or denervation in clinically weak muscles. CSF protein is usually elevated and, unlike the demyelinating neuropathies in the general population a mononuclear pleocytosis of upto 50 cells / mm^3 sometimes occurs[19].

Progressive polyradiculopathy

Since PP was first reported by Eidelberg et al in 1985, it has been increasingly recognized as an alarming complication of AIDS[20]. The disorder is uncommon being reported in fewer than 2% of HIV seropositive patients referred for neurological consultation. Its rapidly progressive course and potentially good response to early therapy demand prompt diagnosis and treatment[20]. PP due to CMV infection occurs in

the setting of advanced systemic HIV disease in patients with very low CD4 cell counts (<50 cells / mm^3) [19].

The clinical presentation of PP in characterized by radiating pain and parasthesias in the cauda equina distribution, followed by rapidly progressive flaccid paraparesis, lower extremity areflexia and mild sensory loss and sphincter dysfunction. The upper extremities may be involved late in the course of polyradiculopathy. The CSF findings in most patients with progressive polyradiculopathy are characterized by marked polymorphonuclear pleocytosis, elevated protein and cultures are positive for CMV in about half of the patients. The most prominent electrophysiologic abnormalities in PP are widespread denervation in lower extremity and lumbar paraspinal muslces, accompanied by abnormal late responses in affected distributions[20]. In most cases PP has a poor prognosis if untreated, with a mortality rate of nearly 100% and a mean duration of illness from onset of neurologic symptoms to death ranging from 2 to 30 days.

Myopathy

Numerous cases of HIV associated myopathy were reported by several groups[21,22]. The predominant presenting symptom of myopathy is slowly progressive muscle weakness, typically characterized by difficulty in rising from a chair or climbing stairs[21]. Myalgia is present in 25 to 50% of affected patients[21]. However, myalgia is a nonspecific symptom in HIV infected individuals and is insufficient for diagnosis of myopathy even in the presence of elevated creatine kinase levels[22]. Electromyography of clinically weak muscles show fibrillation potentials, positive sharp waves, complex repetitive discharge, and a full recruitment of small, short duration motor unit action potentials.

Spinal cord disorders

Vacuolar myelopathy

The most common spinal cord disease complicating HIV infection is HIV associated vacuolar myelopathy[16]. The pathologic finding of noninflammatory vacuolation of myelin, particularly in the lateral and the posterior columns of the spinal cord, characterizes VM. Upper thoracic cord is affected most commonly, but cervical pathology is well described and occasionally diffuse cord changes are seen[16].

The clinical features of HIV-1 related VM have been systematically studied. In an autopsy based clinicopathological correlation, Dal Pan et al[16] found that 15 of 56 patients with pathologically confirmed VM had clinical evidence of myelopathy. Mild to moderate limb weakness were present in all cases, with severe weakness limited to only the most advanced cases. Knee hyperreflexia was common as were lower limb spasticity (eight of 15, 53%) and gait spasticity (60%). A sensory ataxia was seen in 20% of cases. A coexistent distal sensory neuropathy with ankle areflexia or hyporeflexia was also common (eight of 15,53%). A discrete thoracic sensory level was seen in two of 15 cases (13%). Vibration and position sense loss were common. Bowel and bladder dysfunction were seen in only one case. In all cases, the development was slowly progressive, with onset of symptoms ranging from 3 to 16 weeks before the diagnosis of myelopathy. The development of symptomatic myelopathy is more frequent in patients with pathologically more severe VM.

Other causes of myelopathies

Infectious myelopathy

Though the noninflammatory VM is the most common cause of spinal cord disease in HIV-1 infection, there have been several case reports of myelopathy attributed to other infectious agents.

HAM also called tropical spastic paraparesis, has been reported in HIV patients[23] due to HTLV-1 virus.

Other infectious agents resulting in acute myelopathy in HIV patients include Toxoplasma gondii, Treponema pallidum, Herpes viruses and Mycobacterium tuberculosis.

Neoplastic causes of myelopathy due to spinal cord compression from lymphomatous metastasis have been sporadically reported.

INTRACRANIAL OPPORTUNISTIC INFECTIONS

Toxoplasma gondii

Toxoplasma gondii is an ubiquitous obligate intracellular protozoan found throughout the world. For patients with acquired immunodeficiency syndrome, it is the most common cause of focal central nervous system infection. Its incidence appears to be declining among patients receiving Pneumocystis carinii prophylaxis. Earlier reports described frequencies 3 to 40% reflecting considerable regional variation in exposure to the parasite[1,2,24].

In patients with AIDS, over 95% of toxoplasmic encephalitis is due to reactivation of a chronic (latent) infection[24]. For most HIV infected patients, toxoplasmic encephalitis (TE) develops when the CD4 + T lymphocyte count (CD4T count) falls below 100/mm3.

Toxoplasmosis in the AIDS patient is most frequently manifested by toxoplasmic encephalitis, usually alone or less frequently as part of multiorgan infection. Isolated organ involvement without CNS disease is uncommon. TE most frequently presents (50 to 89%) with a subacute onset of neurological deficits with or

without evidence of generalized cerebral dysfunction. Less often (15 to 25%), seizures may be the initial manifestation. The clinical presentation varies from an insidious process evolving over several weeks to a more acute, at times fulminant course. Abnormalities associated with focal lesions include hemiplegia, hemisensory loss, dysphasia, aphasia, movement disorders (hemichorea and hemiballismus), ataxia, diplopia, cranial nerve palsies, cerebellar tremor, severe localized headache, Parkinsonian syndrome, and intractable hiccoughs. Abnormalities attributable to generalized cerebral dysfunction include lethargy, confusion, coma and global cognitive impairment similar to AIDS related dementia[24].

Almost 100% of AIDS patients with TE will have detectable IgG by Sabin Feldman Dye test or immunofluoroscence assay. The ELISA IgM is more sensitive and specific than IFA, but both tests report high false positive results.

CT scan of the brain usually shows multiple ring enhancing lesions with predilection for cortex and deep gray matter structures as the basal ganglia. The cerebellum and brainstem are less commonly involved. MRI is more sensitive than the CT, which can understimate the number of lesions.

Cryptococcus neoformans

Cryptococcus neoformans is the most common fungal infection of the CNS and usually present as a subacute meningitis[25,26]. Cryptococcal disease occurs in 1.9% to 11.6% of patients with AIDS[25,26].

Clinical manifestations can be remarkably benign, with vague malaise or nausea alone. More commonly headache and fever are the presenting features. An acute confusional state can be seen, as can cranial nerve palsies. More specific

symptoms of meningeal involvement such as stiff neck, photophobia, nausea and vomiting are present in only 20 to 40% of patients[25,26].

The CT of the head is normal or shows cerebral atrophy in 75 to 90% of cases. Nonenhancing and contrast enhancing lesions presenting as either nodular or ring like patterns, particularly in the basal ganglia are seen[25,26]. CSF can be normal or show mononuclear pleocytosis, elevated protein, low glucose and high opening pressure. India ink preparations are positive in 72 to 88% of patients. Determination of CSF Cryptococcal Antigen (CRAG) titre is essential because this may be the only CSF abnormality; latex agglutination of CSF for Cryptococcal antigen has a sensitivity of 91% to 100%. A positive CSF culture is the definitive diagnostic test for Cryptococcal meningitis and the main entry criteria in published series. Being the gold standard, its sensitivity approaches by definition 100%[25,26].

Other Fungal Infections

In addition to cryptococcal meningiits, other CNS fungal infections such as Histoplasmosis, Coccidioidomycosis, Blastomycosis and Aspergillosis have been reported.

Progressive multifocal leucoencephalopathy

PML is a demyelinating disease of the central nervous system that results from infection of oligodendrocytes with JC virus, a papovavirus[27]. It affects approximately 4 to 8% of patients with advanced HIV disease[27]. It is a subacute or chronic progressive illness most often characterised by focal neurologic findings such as hemiparesis, gait abnormalities and visual field cuts, and mental status and personality

changes. Dementia, encephalopathy and coma can occur with fulminant disease. Seizures are uncommon, but not rare.

Radiographic imaging provides the strongest support in diagnosing PML but presently confirmation requires brain biopsy. Affecting the white matter, generally not enhancing with contrast and exhibiting no mass effect, the hypodense lesions of PML on CT of the brain reveal areas that may have a "scalloped" appearance as a result of the subcortical fibers lying beneath the cortex[28]. The lesions have a predilection for the frontal and parieto-occipital lobes, may occur virtually anywhere. The brainstem or cerebellum may be solely involved in upto 15% of cases[28].

Demyelination observed with HIV associated dementia may be radiographically indistinguishable from that of PML. Clinically however PML is associated with focal neurological disease and is much more rapidly progressive. Radiographic distinctions include a greater propensity of lesions to involve the subcortical white matter, its hypointensity on T1 weighted images and its rare enhancement[28].

Routine CSF evaluation is nondiagnostic and is usually normal or reveals only nonspecific changes such as mild pleocytosis or protein elevation. CSF PCR detection of JC virus DNA has become the successful tool in the diagnosis of PML.

Viral encephalitis

Herpes simplex virus typically cause acute hemorrhagic necrotizing encephalitis with predilection for subfrontal and medial temporal lobes[29]. In AIDS patients HSV encephalitis presents with typical clinical features which include headache, fever and variable combinations of seizures, behavioral and cognitive

changes, focal signs and ultimately obtundation. Definitive diagnosis often requires brain biopsy, but CSF PCR would reduce the need for tissue diagnosis[29].

Herpes Zoster virus

Herpes zoster virus infection of the nervous system may result in radiculitis. characterized by painful vesicular cutaneous eruptions involving one or several dermatomes[2,3]. It also causes subacute encephalitis in a number of AIDS patients with clinical features which include lethargy, confusion and variable focal findings including cranial neuropathies[30]. Myelitis due to herpes zoster had been described in immunocompromised patients including AIDS patients with clinical features such as subacute progression of motor weakness, sensory deficits and sphincter disturbances in varying combinations that evolve over weeks.

Cytomegalovirus

Of the human herpes viruses, CMV is the major cause of morbidity in AIDS patients and is frequently the cause of death.

CMV encephalitis presents as a subacutely progressive diffuse encephalitis evolving over several weeks and characterized by confusion and imparied sensorium, with variably associated cranial neuropathies, ataxia and motor weakness[31]. Alternatively the presentation may result in focal neurological symptoms corresponding to the location of discrete parenchymal lesions, which may progress to a more diffuse encephalitis[31]. Signs of meningitis may be present[31]. Median survivals following neurological presentation in small series are about a month.

Several recent retrospective studies suggest that polymerase chain reaction amplification technique to detect CMV specific DNA in CSF samples may be a highly sensitive and specific diagnostic test for CMV infection of the CNS.

Necrotizing myelitis attributable to CMV in AIDS presents has been reported by number of authors[32]. Clinical features include paraplegia, urinary retention and hypoesthesia, typical of myelopathy.

CMV poly radiculomyelitis in patients with AIDS presents subacutely with paraesthesias or pain, progressive hypotonic weakness, areflexia and variable sensory deficits ascending from the lower extremities to involve spinal cord, upper extremities and cranial nerves in some patients[32].

Neurotuberculosis

Tuberculosis has become an increasingly common problem in HIV – infected persons and extrapulmonary involvement is seen in 60% of cases. In patients with HIV – related tuberculosis positive CSF cultures are obtained in 3% to 10% of the time[33]. Given the difficulty of culturing this organism from CSF, this implies an even higher rate of CNS complication and typically presents as a subacute meningitis. Headache and fever are noted in the majority of cases with encephalopathy, particularly if there is elevated intracranial pressure. Cranial nerve abnormalities and frank meningeal signs are less common. The CSF analysis usually demonstrates a lymphocytic pleocytosis with a total cell count in the range of 200 to 500/mm^3, hypoglycorrhachia is also commonly observed. Two large series suggest that the clinical presentation, overall CSF profile and prognosis are identical in patients with and without HIV infection. The only difference between seropostive and seronegative patients is an increased incidence of intracerebral mass lesions in the HIV infected group (60% versus 14%).

Isolated CNS tuberculomas may present without concomitant tuberculous meningitis. Their characteristics on cerebral imaging studies have varied; some appears as ring enhancing lesions while others are hypodense and nonenhancing lesions. Anecdotal evidence suggests that CNS tuberculosis may be more common when initial antituberculous therapy has failed, when there is a relapse of disease or when multidrug resistant organisms cause disease. Diagnosis of CNS tuberculosis is still difficult because of the lack of rapid diagnostic tests. Polymerase chain reaction based techniques are used for their purpose. Criteria used for diagnosis of TBM were those previously established by Ogawa et al[34]. A definite diagnosis of TBM was made by isolation of M. tuberculosis from the CSF or the presence of TBM was established

by pleocytosis of the CSF and negative bacterial and fungal cultures (including the determination of bacterial antigens and cryptococcal antigen) and at least one of the following 1) a positive tuberculin skin test; 2) evidence of tuberculosis outside the CNS or previous active tuberculosis; 3) CSF glucose levels less than 2.2 mmol/L (40mg/dl); and (4) CSF protein levels greater than 0.60g/l.

Nontuberculous mycobacterial CNS infections due to Mycobacterium avium complex and Mycobacterium kansasii have also been described.

Bacterial infections

Pyogenic bacterial infections have been increasingly noted over the course of the HIV epidemic and these infections may precede the onset of severe immunodeficiency[35]. Neurological infection with pyogenic bacteria such us pneumococci and nonpyogenic bacteria like Listeria have been reported though it occurs as a very rare event in HIV patients.

NEOPLASMS

Primary CNS Lymphoma

The first reports of PCNSL in HIV infected patients were published with the initial description of AIDS in 1982. Recently, there has been a dramatic increase in the incidence of PCNSL in association with AIDS. It is estimated that 1% to 2% of all HIV infected patients will develop PCNSL[36]. Epstein Barr virus has been implicated as causative for both systemic and primary CNS lymphoma in association with AIDS or other immunocompromised States. The prevalence of EBV in AIDS-associated PCNSL has been reported to range between 94% and 100%[37].

Unlike systemic NHL which can occur at any stage of HIV infection, PCNSL typically occurs in profoundly immunocompromised patients with CD4+ T - lymphocyte counts below 50cells/mm^3 . Alteration in the level of consciousness and focal neurological deficits are the most common presenting signs of PCNSL. Seizures occur in 23% of AIDS patients with PCNSL while cranial nerve deficits are evident in

13%. Signs of increased intracranial pressure are less common. The major difference in presentation between AIDS and non-AIDS related PCNSL are the high prevalence of B symptoms and the shorter duration of symptoms (days to weeks versus months) for patients with HIV related tumors.

Although no radiological finding is pathognomic for PCNSL, some radiological features are suggestive of the diagnosis. A homogenously enhancing lesions in the central gray matter or corpus callosum is highly suggestive of PCNSL. Ring like lesions may occur in 5% to 10% of cases. Most lesions are adjacent to an ependymal or meningeal surface with varying degrees of edema and mass effect. About 50% to 60% of lesions are located peripherally in the hemispheric gray matter or adjacent white matter. Another 25% of the lesions will be found in the deep midline structures of the septum pallucidum, basal ganglia or corpus callosum.

Kaposi's sarcoma

CNS involvement by Kaposi's sarcoma is distinctly unusual. Common signs and symptoms include cranial nerve palsies and polyradiculopathy and less commonly myelopathy due to epidural metastasis with spinal cord compression. Intraparenchymal mass lesions are uncommon[2] .

MISCELLANEOUS

Cerebrovascular complications

HIV infected patients are at increased risk for cerebral infarction. A large study of patients with AIDS (n=1,286) found 1.6% to have cerebrovascular complications[38]. There is a broad spectrum of etiologies, but in many cases the pathogenesis of this is unclear. Cerebral granulomatous angitis due to inflammation in the walls of large and medium sized vessels can result in thrombosis and infarction[39]. Both intracerebral and leptomeningeal arteries may be involved. Varicella zoster infection as well as syphilis may produce cerebral infarction. Nonbacterial thrombotic endocarditis also may be responsible in a number of cases.

CT and MRI may show the sequelae of cerebrovascular disease, including parenchymal haemorrhage, infarction, subarachnoid harmorrhage, and communicating hydrocephalus. Hypodensity is seen on CT, involving both gray and white matter, conforming to a vascular distribution. MRI often demonstrated infarction before detection by CT, with increased signal seen on proton density and T2WIs. Enhancement of arterial structures on MRI may indicate sluggish flow and may be an early sign of infarction[39].

Bell's palsy

Cranial neuropathies are encountered frequently in HIV-1 infection while some patients may develop a cranial neuropathy in the context of a generalized neuropathy, others have developed isolated cranial neuropathies. The most common reports have been facial nerve palsy[40]. An acute lower motor nerve facial palsy, occurs frequently especially in HIV seropositive individuals who are otherwise healthy or who have any constitutional symptoms, such as weight loss, fever or thrush. Facial palsy may also occur during acute aseptic meningitis. Although some of the cases have demonstrated clear evidence of axonal damage, in others it is not clear whether these cases represent central involvement of the facial nerve nucleus, such as may occur in aseptic meningoencephalitis or cranial nerve inflammatory neuropathy per se.

MATERIALS AND METHODS

PLACE OF THE STUDY

This study was conducted at the Government General Hospital, Chennai. Patients admitted to the wards of the institute of internal medicine and neurology wards were subjects of the study.

PERIOD OF STUDY

APRIL 2005 - AUGUST 2006

DESIGN

Prospective Randomised cross sectional study.

METHODOLOGY

HIV patients admitted at Government General Hospital were Chosen for the study, Random selection of patients were made in whom a detailed history and clinical evaluation which included the mini mental score (MMSE) was done, after an informed consent from the patient or relative.

The following investigation were done to all patients studied (i.e), when tested positive for HIV.

1. Complete blood count.
2. Renal function test (Sugar, Urea, Creatinine and Electrolytes)
3. Liver Function Test (Bilirubin, AST, ALT, SAP, Albumin)
4. Chest X-ray - P.A View

All patients with neurological systems were individualised and were subjected to the investigation listed based on clinical findings.

1. C.S.F.
2. CT Brain
3. MRI Brain
4. Nerve Conduction Study
5. Creatinine Phosphokinase
6. Electro Encephalogram (EEG)
7. VDRL

METHODOLOGY OF INVESTIGATION

HIV Serology was done using Microlisa Kit.

CD_4 count were done with Facs Count (Automated Counter) manufactured by Becton and Dickinson.

Tests were done in a single laboratory by the same person, no intrpersonal error was possible. The VCTC laboratory in our college in a laboratory identified by NACO.

EXCLUSION CRITERIA

Immuno Compromised state due to any other cause.

LIMITATIONS

- Culture and PCR for mycobacterium could not be done.
- Viral Serology was done only in selected patients.

RESULTS AND OBSERVATIONS

INCIDENCE

32 Patients had neurological manifestations among the 100 Patients studied. The incidence of neurological manifestations in HIV infection, in this study is 32%

SEX DISTRIBUTION

Of the 100 Patients studied 75 were male and 25 were Female. Among the 75 males, 29 had neurological manifestations and of the 25 Females, 3 had neurological Symptoms.

TABLE NO.1 - shows the sex distribution in this study

Sex	Positive	Negative	Total
Male	29 38.7%	46 61.3%	75 75%
Female	3 12.0%	22 88.0%	25 25%

AGE DISTRIBUTION

TABLE NO.2 - shows the age distribution in this study

Age in Years	Positive	Negative	Total
<30	5 25%	15 75%	20
31-40	19 31.6%	41 68.3%	60
>40	8 40.0%	12 60.0%	20

Majority of the patients in our study were between 31-40 yrs of age. Of the 60 Patients, who were in the age group of 31-40, 19 (31.6%) had neurological symptoms.

OCCUPATION

TABLE NO.3 : shows the various occupations involved in this study

Occupation	Positive	Negative	Total
Agriculture	3 33.33%	6 66.66%	9
Daily Labourer	12 37.50%	20 62.50%	32
Driver	5 33.33%	10 66.66%	15
House Wife	3 17.64%	14 82.35%	17
Mechanic	2 50.008%	2 50.00%	4
Painter	4 28.57%	10 71.42%	14
Unemployed	3 100%	0	3
Student	0	1 100%	1
Business	0	4 100%	4
Accountant	0	1 100	1

In our study most of the patients were daily wage earners (32%) and neurological symptoms were also Common among these group of patients.

MODE OF TRANSMISSION

All Patients in this study group had Hetero Sexual behaviour as the mode of transmission. One Patient had I.V. drug usage as risk factor along with heterosexual behaviour.

TABLE NO.4

Mode of Transmission	Frequency	Percentage
Hetro Sexual	100	100%
Homo Sexual	-	-
I.V. Drug abuse	1	1%

PRE - EXISTING INFECTION

Among 32 Patients who had neurological symptoms, 1 Patient had TB adenitis as co infection.

TABLE NO.5

Co Infection	Frequency	Percentage
TBA	1	3.13%
Nil	31	96.88%

PHYSICAL ACTIVITY STATUS IN PATIENTS WITH NEUROLOGICAL SYMPTOM

TABLE NO.6

	Frequency	Percentage
Ambulatory	19	59.38%
Working	9	28.13%
Bed Ridden	4	12.50%

19 Patients in the study group who had neurological manifestation were Ambulatory (i.e. able to do their daily activities but not working), 9 were working and 4 were bed ridden.

CLINICAL PRESENTATIONS

This table shows the various Clinical Presentations and their frequency in the Patients having neurological Manifestations.

TABLE NO.7

Clinical Presentation	Frequency	Percentage
Headache	13	40.03%
Altered Sensorium	14	43.75%
Hemiplegia	4	12.50%
Seizures	8	25.00%
Paraperesis	4	12.50%
Quadriperesis	1	3.13%
Parasesthesias	2	6.25%
Cerebellar Syndrome	2	6.25%
Involuntary Movements	1	3.13%

CHART - 1 : Shows various diseases presenting as Altered Mentation in this study

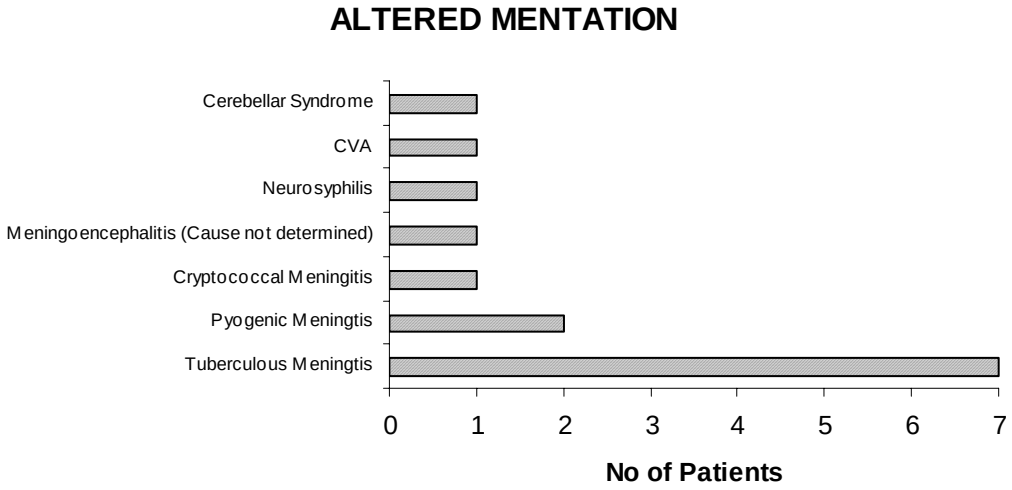


CHART - 2 : Shows various diseases presenting as Headache in this study

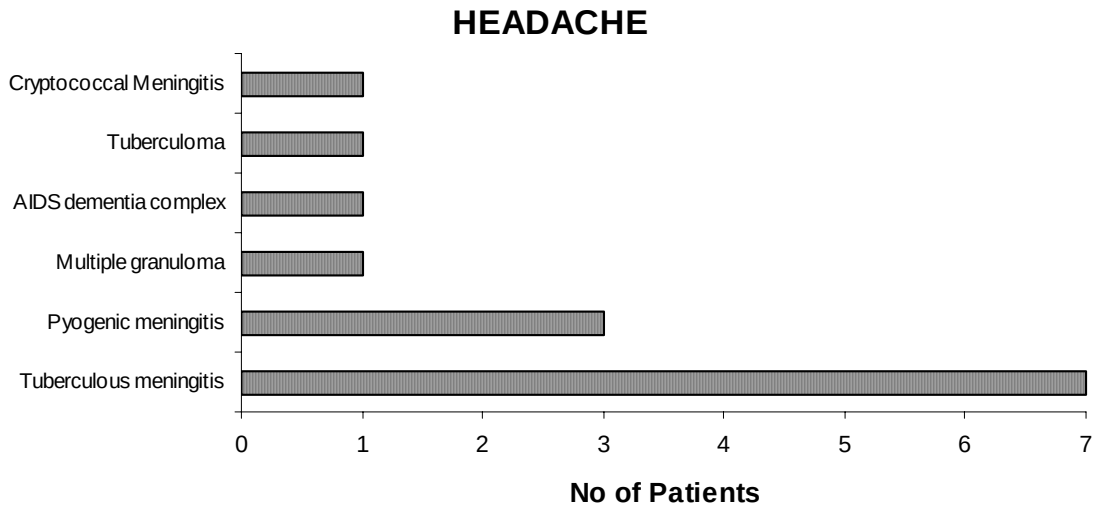


CHART - 3: Shows various diseases presenting as Hemiplegia in this study

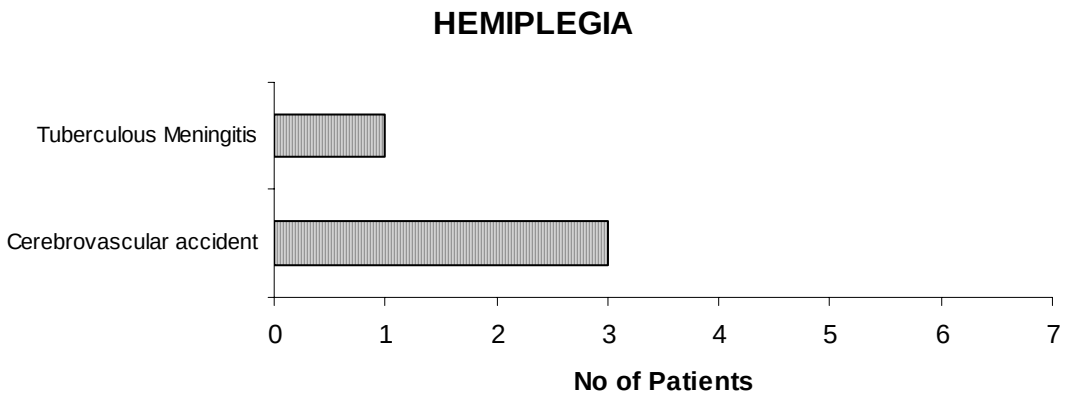
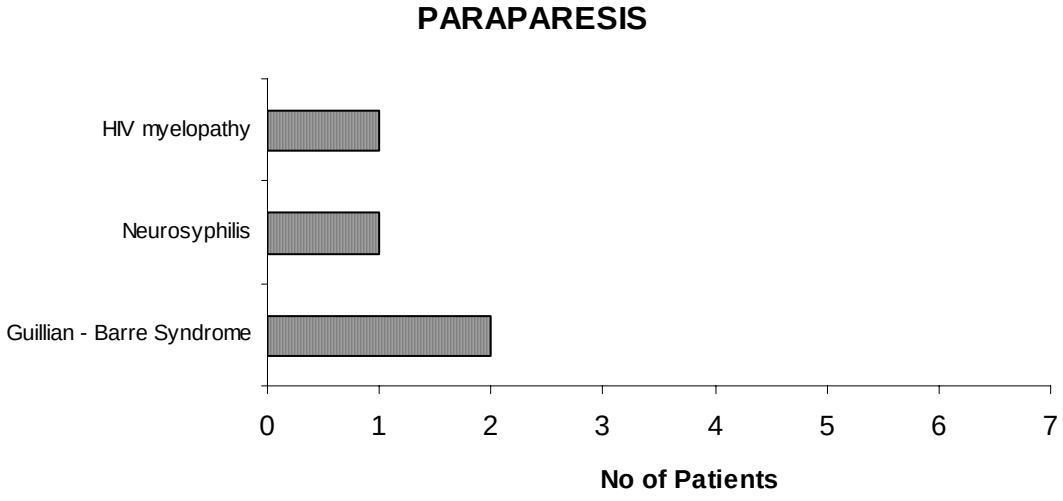


CHART - 4 : Shows various diseases presenting as Seizures in this study

CHART - 5 : Shows various diseases presenting as Paraparesis in this study



DISEASE PATTERN

Shows the disease patterns among patients who had neurological manifestations.

TABLE NO.8

Diagnosis	Frequency	Percentage
Acute Flaccid Paralysis	1	3.13%
AIDS Dementia Complex	1	3.13%
Cerebellar Syndrome	1	3.13%
Cryptococcal Meningitis	1	3.13%
Cerebrovascular Accident	3	9.38%
Guillian Barre Syndrome	2	6.25%
HIV Myelopathy	1	3.13%
Meningoencephalitis (Cause not determined)	1	3.13%
Multiple Granuloma	1	3.13%
Myopathy	1	3.13%
Neurosyphils	1	3.13%
Peripheral Neuropathy	2	6.25%
Progressive Multifocal Leucoencephalopathy	1	3.13%
Pyogenic Meningitis	2	6.25%
Seizure Disorder	2	6.25%
TB Meningitis	10	31.25%
Tuberculoma	1	3.13%

OUT COME

TABLE NO.9 : shows the outcome in the study

Out Come	Frequency	Percentage
Expired	18	56.25%
No. Improvement	9	28.13%
Improved	5	15.63%

18 Patients who had neurological manifestations in the study group expired (56.25%), 9 Patients showed no improvement (28.13%) and 5 Patients had improvement in their clinical condition.

CD_4 COUNT CORRELATION

TABLE NO.10

	CD_4 Count	
	Mean	**SD**
Patient with Neurological Manifestation	179.19	113.16
Patient without neurological Manifestation	225.03	134.58

CD_4 count levels in Patients with neurological manifestations ranged from 9 and 539 with an average of 179.19. The average CD_4 levels in Patients without neurological manifestations was 225.03. There was no statistically significant difference between the two groups. (P>0.05)

CD_4 CORRELATION WITH MORTALITY

TABLE NO.11

Out Come	**CD_4 Count Mean**	**SD**
Expired	108.38	41.65
No Improvement	231.78	128.87
Improved	268.60	110.94

The mean CD_4 Count of the patients who expired was 108.38. Mean CD_4 Count of the patients who did not improve and who improved were 231.78 and 268.60

respectively. There is a statistically significant correlation of CD_4 count among patients who expired (P-0.003**).

CD_4 CORRELATION WITH TB MENINGITIS

There were 10 Patients diagnosed to have TB Meningitis. CD_4 Count for one Patient was not done as the patient died before blood was taken for CD_4 count. The mean CD_4 count of patients with TB Meningitis in the study group was 120.88 and the mean CD_4 count of patients who did not have any neurological manifestations was 225.02. Statistically significant different of CD_4 count was observed between the two groups. (P-0.025*).

TABLE NO.12

	No. of Cases	**Mean**	**SD**
Patients with TB Meningitis	9	120.88	43.161
Patients without Neurological Manifestation	68	225.02	134.585

MINI MENTAL SCORE

TABLE NO.13

	MMSE	
	Mean	**SD**
Patient with Neurological Manifestation	24.94	2.13
Patient without neurological Symptoms	26.65	.84

Mini mental Score of Patients with neurological symptoms was compared with those without neurological symptoms. Significant difference was observed in patients with neurological symptoms, P value being less than 0.001**

FUNDUS

Fundus Examination was done for all co-operative patients.

6 patients had features of papilloedema and one patient had features of HIV Retinitis.

CSF ANALYSIS

CSF Analysis was done for 22 patients in the study.

11 Patients had elevated proteins and predominant lymphocytes.

5 Patients had normal CSF.

2 had elevated proteins and acellular smear.

2 had elevated proteins and predominant neutrophils.

1 had elevated proteins and occasional lymphocytes and also had positivity for cryptococcus in India Ink preparation.

CT BRAIN

26 Patients in the study were subjected to CT Brain among which 3 patients had middle cerebral arterial territory infarct, 1 had left cerebellar hypodensity and 1 had multiple calcified granulomata.

MRI

In this study 3 patients had MRI brain done for them. 1 had extensive white matter lesions suggesting PML, 1 had multiple ring enhancing lesions who was diagnosed to have Tuberculoma and other patient had features suggestive of normal pressure hydrocephalus.

DISCUSSION

In this study, of the 100 seropositive patients, 32 had neurological manifestations (32%). The incidence of neurological manifestations in HIV positive patients according to snider et al[1] was 31% and levy et al[2] was 39%. In India Gupta et al[41] found an incidence of 25.75% in his study.

AGE

Most of the patients in this study were in the age group of 31 – 40 (59.38%). The mean age of the patients with neurological manifestations in a study in university of California and Sanfransisco data was 37.3 years[38]. Mean age in this study was 35.63 years.

SEX

Male patients were found to have neurological manifestations more common (90.63%) as against females (9.38%). Male to female ratio was approximately 9:1. Mehta et al has reported male predominance with male to female ratio of 12:1.

OCCUPATION

High incidence of neurological manifestations was noted among daily wage labourers (37.50%), followed by drivers with 15.63%. Perhaps these patients more often seek medical help in government hospital and also because HIV infection rate are high in this group of patients.

MODE OF TRANSMISSION

All patients with neurological manifestations had heterosexual behaviour as the risk factor. None of our patients had homosexual relationship. Gupta et al[41] found heterosexual relationship in 64.7%, 5.85% in drug abusers and blood transfusion in 14.7%.

PRE-EXISTING INFECTION

Tuberculous adenitis was present in one patient with tuberculous meningitis. Patient had enlarged cervical lymphnodes on presentation and was not on antiretroviral therapy. So, a possibility of immunomodulation syndrome was unlikely.

CLINICAL PRESENTATION

ALTERED SENSORIUM

This was the commonest presenting symptom in the study. 14 out of the 32 patients, had altered sensorium (43.75%). Altered sensorium as observed in this study was primarily due to a meningeal infection, tuberculous meningitis being most frequent, followed by cryptococcal and pyogenic meningitis. None of the patients in this study had CNS lymphoma. University of California and Sanfransisco data revealed altered sensorium as a manifestation in secondary viral infection. Progressive multifocal leucoencephalopathy, toxoplasmosis, cryptococcosis, HIV dementia and lymphoma[38].

HEADACHE

13 of the 32 patients with neurological symptoms, presented with headache (40.63%). 11 patients (84.61%) had opportunistic infections like tuberculous meningitis, cryptococcosis and pyogenic meningitis as the cause. Two other patients had HIV dementia and multiple granulomata as the cause.

Headache is an extremely common symptom in HIV infection, because of the frequency of intracranial infection and mass lesions. CB Graham et al[42] has described headache as a common symptom in HIV infection frequently.

SEIZURES

In our study, the common cause for seizures was neurotuberculosis. Of the 32 patients, 8 patients had seizures (25.00%). Two patients had normal CT brain and

C.S.F analysis did not reveal any abnormality. EEG in these patients showed bilateral epileptiform activity.

This is perhaps because approximately half the HIV infected patients have no definite identifiable disease of the brain and cerebral HIV infection seems to be the likely cause of the seizures, as reported by Holtzman et al study which had HIV encephalopathy as the cause of seizures in 24% of the patients[43].

PARAPARESIS

4 patients had paraparesis on presentation in our study (12.50%). Of the 4, 2 were due Guillian - Barre syndrome, one due to HIV myelopathy and one had concomitant neurosyphilis.

Human T cell lymphotrophic virus 1, tuberculosis, herpes zoster and syphilis were the causes of paraparesis described by A.I Bhigjee et al in their study[44].

PARAESTHESIAS

Two patients in our study had paraesthesias of both lower limb (6.25%). Electrodiagnostic study done in these two patients showed slowing of sensory conduction of lower limb sensory nerves. Both the patients were on antiretroviral therapy (which included zidovudine) and improved with amitryptilline and nutritional support.

Gupta et al has shown an incidence of 8.82% of peripheral neuropathy in his study[41].

CEREBELLAR SYNDROME

Of the 32 patients 2 had features of cerebellar syndrome (6.25%). One patient had an hypodense lesion in the cerebellar area in the CT brain (plain) and the other patient had VDRL positive both in C.S.F analysis and blood i.e associated neurosyphilis.

Mc Arthur et al had noticed gait disturbance and clumsiness in 45% of patients with HIV dementia[45]. Both our patients did not have associated dementia.

INVOLUNTARY MOVEMENTS

One patient had involuntary movements in this study. He had abnormal semipurposive movements involving right upper limb and abnormal flinging movements of the lower limbs. MRI of the patient showed extensive white matter lesions. Patient was diagnosed as progressive multifocal leucoencephalopathy. PCR for JC virus however could not be done.

PITAGORAS DE MATTOS JAMES et al[46] has showed an incidence of 2.7% for involuntary movements in HIV. Almost all types of involuntary movements have been reported in HIV, of which the most common was secondary to parkinsonism.

Comparative Table : 1

	Bandyopadhyay et al	**This study**
Number of Patients	128	100
Incidence	32.9 %	32 %
Headache	N.A	13 (40.63%)
Altered sensorium	14 (8.9%)	14 (43.75%)

Hemiplegia	N.A	4 (12.50%)
Seizues	17 (10.8%)	8 (25.0%)
Paraparesis	N.A	1 (3.13%)
Paraesthesias	N.A	2 (6.25%)
Cerebellar Syndrome	N.A	2 (6.25%)
Involuntary Movements	N.A	1 (3.13%)
Psychosis	11 (6.3%)	N.A

* N.A - Not available

AIDS DEMENTIA COMPLEX

Among the 32 patients, one had AIDS dementia complex (3.13%). Patient presented with headache and progressive cognitive decline. Mini mental score of the patient was 22. CT brain and C.S.F analysis were normal.

Impaired memory and concentration with psychomotor slowing represent the common early presentation of this disorder.

Bandyopadhyay et al[47] reported 21% incidence in their studies respectively. In view of these findings baseline MMSE is probably advisable for all cases with HIV seropositivity and periodic evaluation may unearth more cases with AIDS dementia complex.

PERIPHERAL NEUROPATHY

In our study two patients had peripheral neuropathy (6.25%). Both the patients presented with paraesthesias and was taking antiretroviral therapy which included

zidovudine. Nerve conduction study in both these patients revealed slowing of sensory conduction at lower limb sensory nerves.

HIV associated sensory neuropathies include both distal sensory polyneuropathy due to HIV infection and antiretroviral toxicity. It is very difficult to differentiate between the two[48]. Treatment is largely symptomatic. Our patients improved with change of retroviral regimen, amitryptilline and nutritional support.

MYOPATHY

One patient in our study had myopathy (3.13%). The patient presented with myalgia, proximal muscle weakness. On investigating further he had elevated creatinine kinase levels. Patient was on antiretroviral therapy, whether the myopathy was due to the primary infection or antiretroviral therapy could not be established as the patient refused a muscle biopsy. After stopping zidovudine patient was followed up, but showed no improvement in symptoms.

Studies have suggested that zidovudine induced myopathy occurs only when an underlying HIV related inflammatory myopathy is present[49].

HIV MYELOPATHY

Of the 32 patients in the study, one had HIV related myelopathy (3.13%). Patient had lower limb weakness and urinary incontinence on presentation. MRI spine showed no abnormalities and C.S.F analysis was normal. Vitamin B12 levels were done to rule out a secondary cause, which was also normal.

Jerez.p et al[50] have shown 22% incidence of spinal lesions in AIDS. Leading cause of myelopathies described in association with HIV was vacuolar myelopathy followed by myelitis.

NEUROTUBERCULOSIS

11 out of 32 patients who had neurological symptoms in our study had tuberculous infection of the nervous system. Among the 11 patients, 10 had tuberculous meningitis (31.25%) and 1 had tuberculoma (3.13%). 9 of the 10 patients with tuberculous meningitis expired (90%).

The patient diagnosed with tuberculoma presented with headache and partial seizures involving left upper limb. MRI brain revealed multiple ring enhancing lesions. C.S.F analysis showed elevated protein with predominant lymphocytes.

Increased number of neurotuberculosis in Indian studies is probably due to the high prevalence of tuberculosis in this part of the world.

In all our patients tuberculous meningitis was the first manifestation of the disease. None of the patients were on antiretroviral therapy.

PYOGENIC MENINGITIS

2 patients had features of pyogenic meningitis (6.25%). Both the patients presented with altered sensorium, fever and headache. CT brain was normal and C.S.F analysis revealed elevated proteins and predominant neutrophils in cytology. C.S.F culture did not grow any organism.

Both the patients however succumbed to the disease proving the point that pyogenic infection coexisting with HIV infection has very high mortality.

AIDS related CNS complication from bacterial pathogens have not been reported from western studies.

Studies from third world countries, such as that of baingana et al[51] from Uganda reported 7% incidence of bacterial meningitis.

CRYPTOCOCCAL MANINGITIS

Of the 32 patients one had cryptococcal meningitis (3.13%). Headache, altered sensorium and signs of meningeal irritation was the presentation. C.S.F analysis in this patient was positive for Cryptococcus on India ink preparation.

Bandypadhyay et al[47] in his study had 3.7% incidence of cryptococcal meningitis.

PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

One patient in our study was diagnosed to have progressive multifocal leucoencephalopathy (3.13%). The patient had involuntary movements involving right upper and lower limbs with memory loss on presentation. Mini mental score of the patient was 20. C.S.F analysis showed no abnormalities. MRI brain revealed extensive white matter lesions involving left caudate nucleas, capsuloganglionic region, bilateral parietal and occipital regions, with enhancement on T2W flair image.

Snider et al[1] studied 50 patients with AIDS, in which he had 2 patients with progressive multifical leucoencephalopathy.

NEUROSYPHILIS

In our study one patient had concomitant neurosyphilis(3.13%). Patient presented with unsteady gait, bladder incontinence and subacute onset of paraparesis on admission. On examination patient had anisocoria with right pupil dilated exhibiting Argyll Robertson phenomenon. Blood and C.S.F VDRL was reactive (1 in 64 dilutions and 1 in 8 dilutions respectively). C.S.F for TPHA was positive. MRI of the spine was normal and nerve conduction studies in lower limbs was abnormal suggestive of polyradiculoneuropathy.

Bordon J et al[52] studied 972 HIV seropositive patients over the period of 3.5 years and found an incidence of 3.1% for concomitant neurosyphilis.

CEREBROVASCULAR ACCIDENT

3 patients in our study presented with cerebrovascular complications (9.38%). All three patients presented with hemiparesis and their CT brain showed middle cerebral arterial territory infarct. One of the patient had a poor GCS (6/15). On admission and he expired on the same day. Evaluation of the other 2 for young stroke showed no abnormalities.

Gupta et al[41] has reported 8.82% incidence of CVA in seropositive patients in his study.

There is a broad spectrum of etiologies causing this scenario but in many cases the pathogenesis is unclear. Cerebral granulomatous angitis due to HIV infection could result in vascular occlusive disease[39]

.

GUILLIAN BARRE SYNDROME

Among the 32 patients with neurological symptoms, 2 had Guillian - Barre syndrome (6.25%). Both the patients presented with features of ascending paralysis. C.S.F analysis showed elevated protein with acellular smear cytology. Nerve conduction studies had features of axonal degeneration. Oligoclonal band in C.S.F could not be done.

HIV-GBS occurs in early and late stages of HIV infection, and may follow onset of AIDS. TH Brannagan et al[53] had reviewed 10 patients with HIV-GBS between 1986 and 1999, in which GBS was the first symptom of the HIV infection in 3 patients.

SEIZURE DISORDERS

Two patients in this study group presented as seizure disorder (6.25%). One patient presented with left focal seizure involving upper limb with secondary generalization and the other patient had generalized tonic clonic seizures. CT brain and C.S.F analysis were normal in both the patients. EEG showed bilateral epileptiform activity.

Approximately half of HIV infected patients with seizures have no definite identifiable disease of the brain and cerebral HIV infection seems to be the most likely cause of the seizures. It the study by Holtzman et al, HIV encephalopathy was responsible for seizures in 24% of the patients[43].

MULTIPLE GRANULOMATA

In our study one patient presented with chronic headache of 2 years duration. CT brain done on the patient showed multiple calcified granulomas. C.S.F analysis revealed no abnormality. As the patient could not afford MRI brain was not done. Patient was empirically treated with albendazole with no apparent improvement on immediate follow up.

MORTALITY

18 out of the 32 patients who had neurological manifestations expired in our study (56.25%). Half of the deaths were due to tuberculous meningitis (50.00%).

Morbidity and mortality in HIV/AIDS is well established. Co-existing neurological manifestations appear to significantly contribute to poor outcome.

Comparative Table : 2

	Gupta et al	**Bandyopadhyay et al**	**Our study**
Year of Study	1993	2005	2006
Incidence	25.75%	32.9%	32%
Mode of transmission	Heterosexual - 64.5% I.V Drug abuser - 5.85 % Blood transfusion - 14.7 %	N.A	Heterosexual - 100%
AIDS dementia complex	17.65%	13.3%	3.13%

Peripheral neuropathy	8.82%	8.2%	6.25%
Neurotuberculosis	58.82%	12.1%	31.25%
Cryptococcal meningitis	8.8%	6.0%	3.13%
Neurosyphilis	N.A	N.A	3.13%
PML	N.A	N.A	3.13%
Myopathy	N.A	N.A	3.13%
Toxoplasmosis	3.8%	2.5%	-
CVA	8.82%	N.A	9.38%
Seizure disorder	N.A	N.A	6.25%

Figure - 1 : MRI Brain showing extensive white matter lesions (PML)

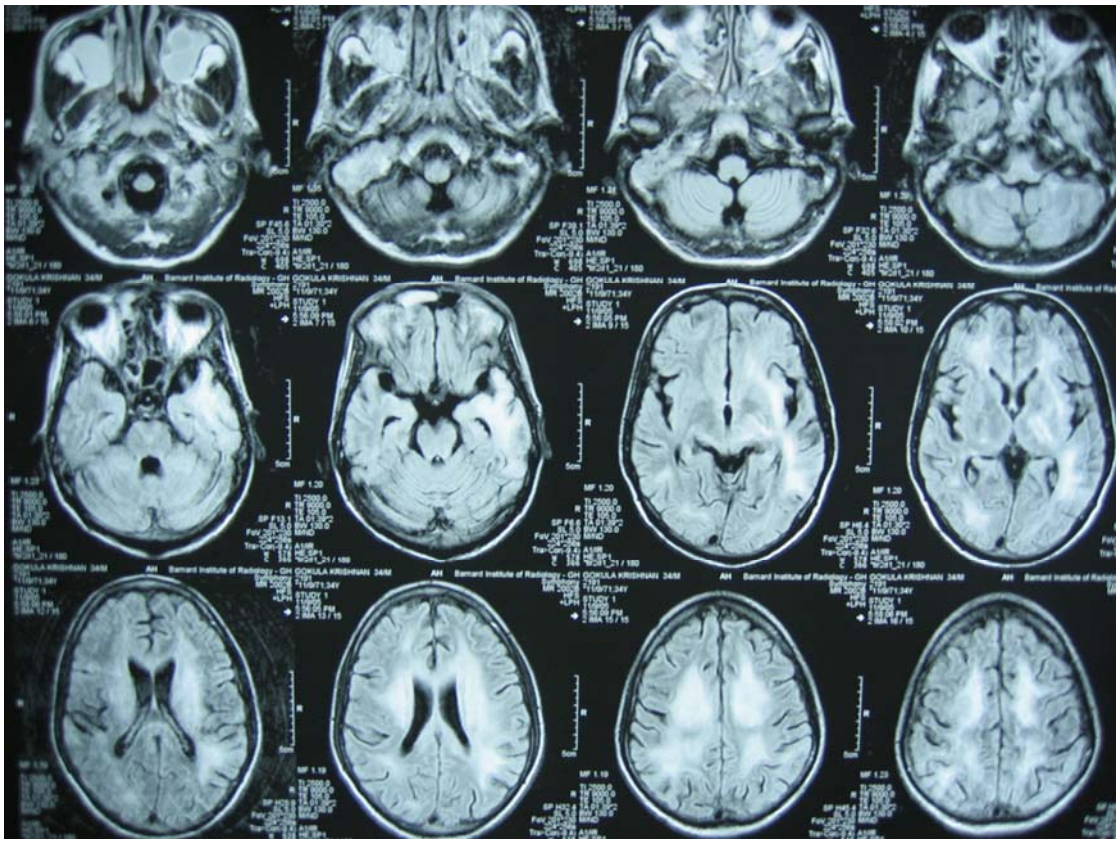


Figure - 2 : MRI Brain (Saggital section) showing extensive white matter lesions (PML)

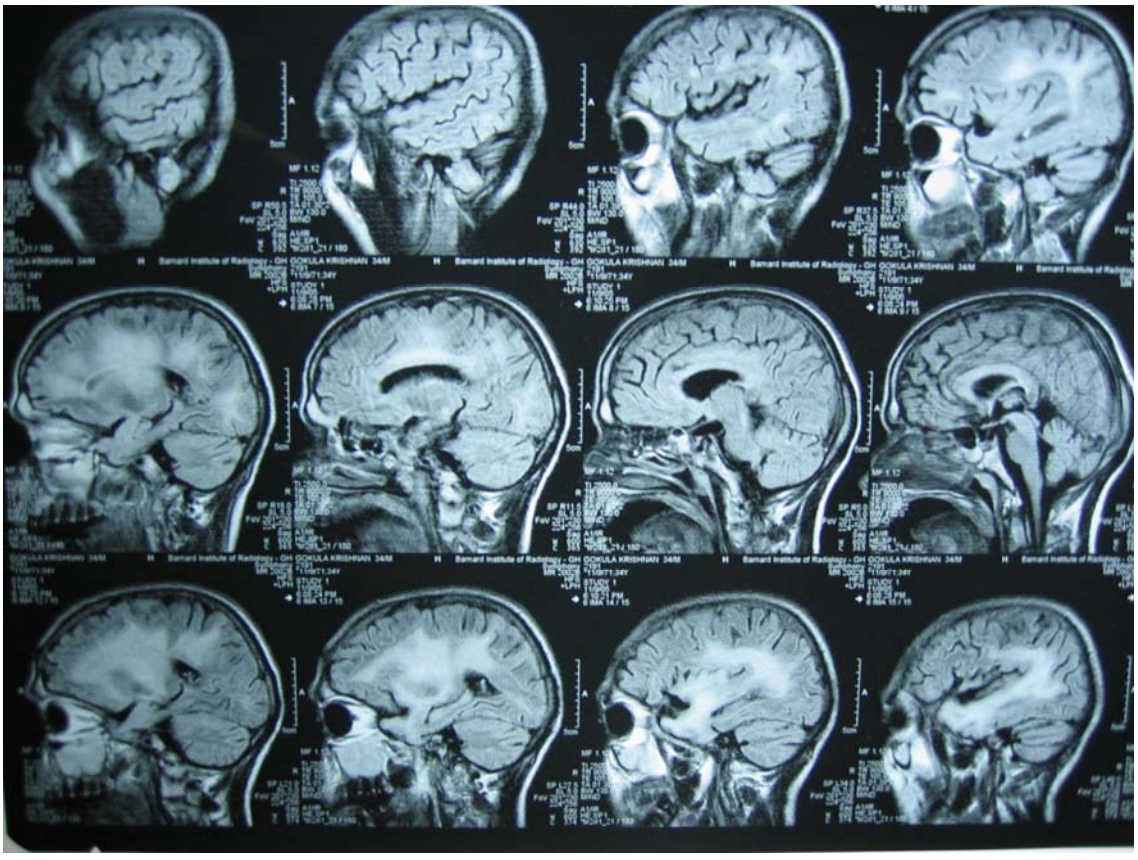


Figure - 3 : MRI Brain showing ring enhancing lesions (Tuberculoma)

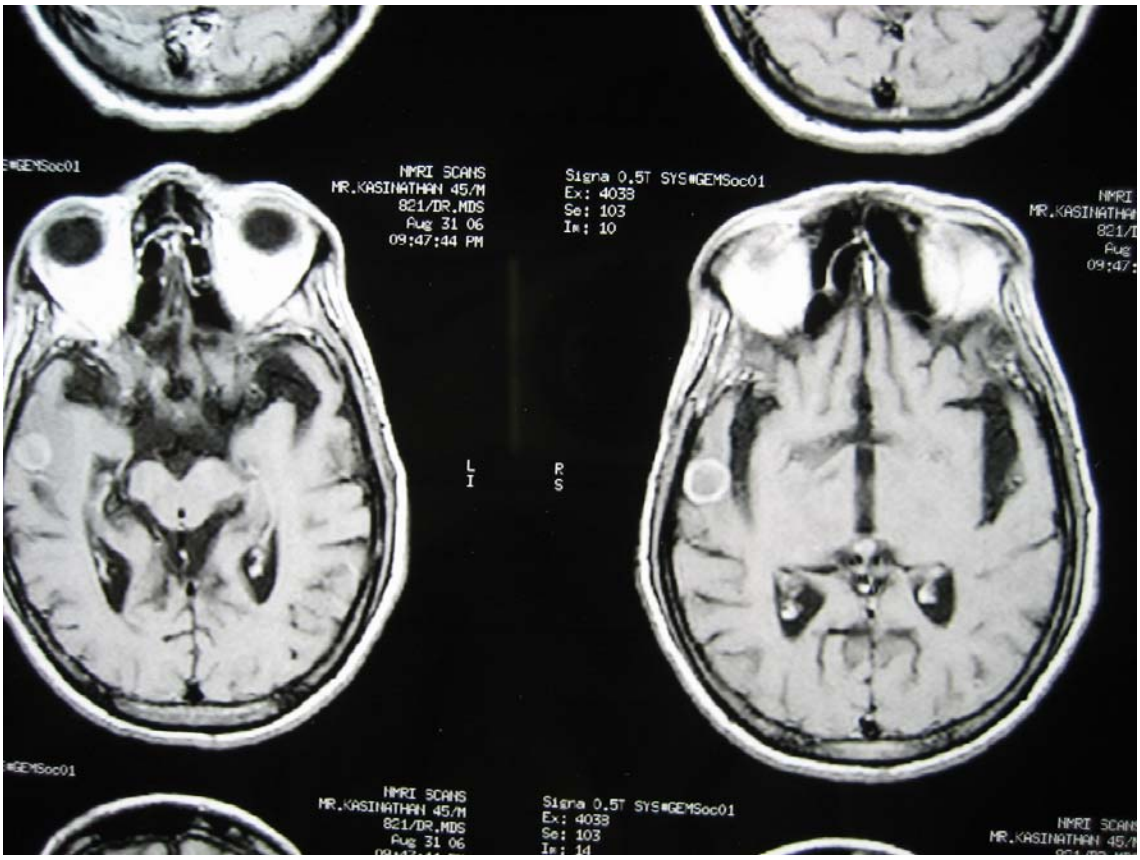
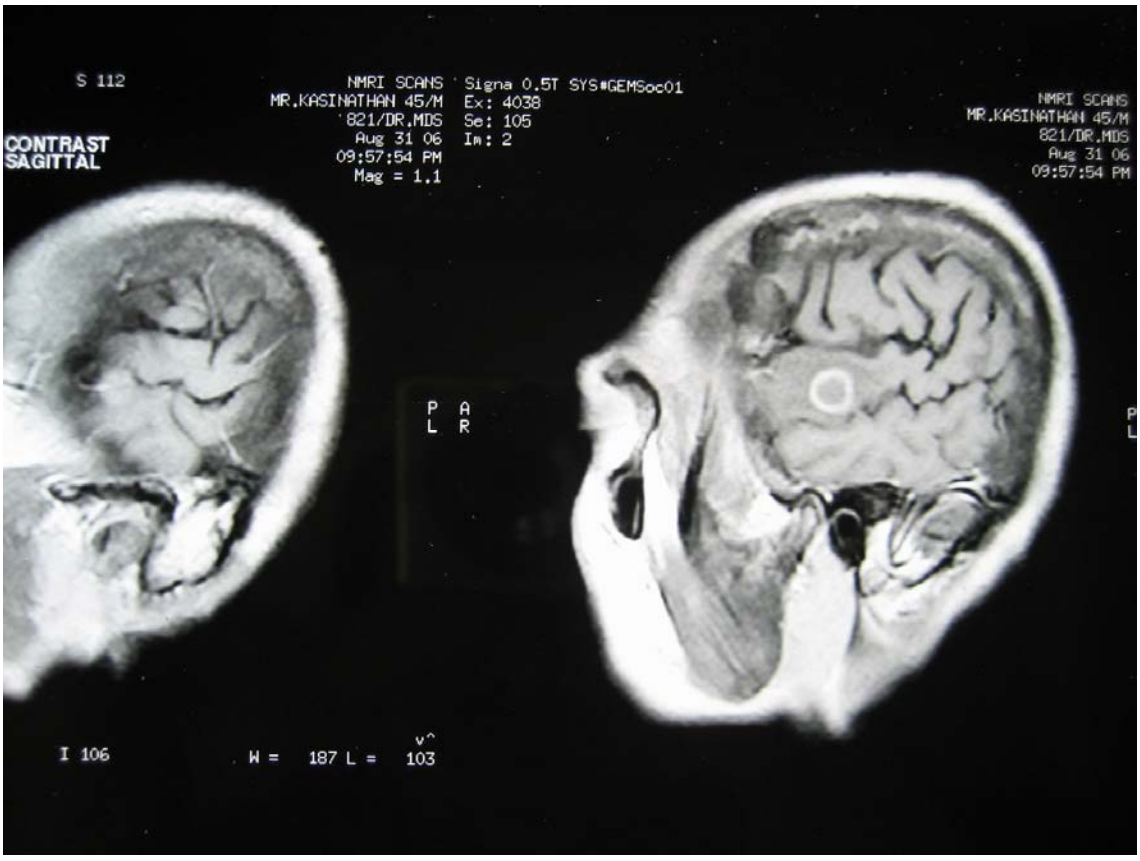


Figure - 4 : MRI Brain (saggital section) showing ring enhancing lesions (Tuberculoma)



CONCLUSIONS

1. Incidence of neurological illness in HIV infection in our study was 32%.

2. Altered mentation and seizures were the two common symptoms observed in this study.

3. All patients in our study had heterosexual transmission of disease.

4. CNS manifestations in men were more common than in women.

5. Tuberculous meningitis was the most commonest opportunistic infection in our study.

6. No significant CD4 count correlation was found between the patients with neurological manifestations and those without neurological manifestations.

7. Patients with neurological manifestations had high mortality and poor outcome.

8. Tuberculous and pyogenic meningitis were associated with very high mortality.

9. CD4 count when less was associated with increased mortality.

10. Patients with coexisting tuberculous meningitis and HIV injury had significantly lower CD4 counts.

SUMMARY

Of the 100 patients 32 had neurological manifestations.

Following were the neurological manifestations : Tuberculous meningitis(31.25%), cerebrovascular complications(9.38%), Guillian barre syndrome (6.25%), pyogenic meningitis (3.13%), peripheral neuropathy (6.25%), seizure disorders (6.25%), acute flaccid paralysis (3.13%), AIDS dementia complex (3.13%), cerebellar syndrome (3.13%), cryptococcal meningitis (3.13%), HIV myelopathy (3.13%), meningoencephalitis – cause not determined (3.13%), multiple granulomata (3.13%), myopathy (3.13%), neurosyphilis (3.13%), progressive multifocal leucoencephalopathy (3.13%), Tuberculoma (3.13%).

Mortality increased most with coexisting Tuberculosis and with decreased CD4 counts.

Commonest neurological condition associated was neurotuberculosis.

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PROFORMA

Name : Age : Sex :

Place : Occupation : Date of Admission :

Hospital No : Date of Discharge :

PRESENTING COMPLAINTS :

Past History : Yes No

Diabetes Mellitus

Hypertension

H/O Tuberculosis

H/O Exposure to a case of tuberculosis

PERSONAL HISTORY :

Marital Status :

Diet : Appetite : Sleep :

Bowel : Bladder :

Habit : Alcohol Yes No

Smoking Yes No

Tobacco Chewing Yes No

RISK FACTORS	YES	NO
Heterosexual		
Homosexual		
I.V drug abuser		

GENERAL PHYSICAL EXAMINATION :

Built & Nourishment :

Pallor : Icterus : Cyanosis :

Clubbing :

Pedal edema : Lymph nodes :

Oral Candidiasis :

Herpes Zoster :

Glossitis :

VITAL SIGNS :

Pulse :

Blood Pressure :

Temperature :

Respiratory Rate :

Weight :

NERVOUS SYSTEM EXAMINATION :

HIGHER MENTAL FUNCTIONS :

MINI MENTAL STATE EXAMINATION SCORE :

CRANIAL NERVES :

FUNDUS :

MOTOR SYSTEM EXAMINATION : UPPER LIMB

LOWER LIMB

REFLEXES : SUPERFICIAL REFLEXES

DEEP TENDON REFLEXES

CO-ORDINATION :

INVOLUNTARY MOVEMENTS :

SENSORY SYSTEM EXAMINATION :

PRIMITIVE REFLEXES :

SIGNS OF MENINGEAL IRRITATION :

GAIT :

SKULL & SPINE :

PERIPHERAL NERVES :

OTHER SYSTEMS : CVS

RS

PA

INVESTIGATIONS :

Hb
TC
DC
ESR
Urine Routine
LFT
RFT
Serum Electrolytes
Blood Sugar
Chest X-Ray

Sputum Examination

CEREBROSPINAL FLUID STUDY :

Cell - Count
Type

Proteins

Sugar

Staining

Culture

Others

SPECIAL INVESTIGATIONS:

FINAL DIAGNOSIS :

COURSE IN THE HOSPITAL

ABBREVIATIONS

ADL	-	Activity of daily living
AIDP	-	Acute inflammatory demyelinating polyneuropathy
AIDS	-	Acquired immunodeficiency syndrome
CIDP	-	Chronic inflammatory demyelinating polyneuropathy
CMV	-	Cytomegalovirus
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
CVA	-	Cerebrovascular Accident
ddI	-	dideoxyinosine
ddC	-	dideoxycytidine
d4T	-	Stavudine
DSP	-	Distal symmetric polyneuropathy
ELISA	-	Enzyme linked immunosorbant assay
GBS	-	Guillian - Barre Syndrome
HAM	-	HIV associated myelopathy
HIV	-	Human immunodeficiency virus
HTLV-1	-	Human 'T' cell lymphotropic virus
HSV	-	Herpes simplex virus
IFA	-	Immunofluoroscence assay
IL	-	Interleukin
JC	-	Cruezfeld Jacob
MRI	-	Magnetic resonance imagining
MM	-	Mononeuropathy multiplex
NACO	-	National AIDS Control Organization
NCV	-	Nerve conduction velocity
PCR	-	Polymerase chain reaction
PCNSL	-	Primary CNS Lymphoma
PP	-	Progressive polyradiculopathy
PML	-	Progressive multifocal leucoencephalopathy
TBM	-	Tuberculous meningitis
T_2WIs	-	T_2 weighted images
TNF	-	Tumour necrosis factor
TGF	-	Transforming growth factor
VM	-	Vacuolar myelopathy

S.No	Name	Age	Sex	Occ	M.O.T	C.I.	P.A.S	H	A.S	Hem	S	P	Q	Pa	CS	I.M	CD4	MMSE	F	C.S.F	CT	MRI	Diagnosis
1	Sumithra	28	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	-	164	28					
2	Jayavel	36	M	D.L	H.S.	-	A	-	-	-	-	-	-	-	-	-	176	27					
3	Elango	38	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	224	26					
4	Chandran	37	M	AGR	H.S.	-	W	-	-	-	-	-	-	-	-	-	211	26					
5	Upendran	27	M	STU	H.S.	PTB	A	-	-	-	-	-	-	-	-	-	50	25					
6	Damotharan	38	M	D.L	H.S./I.V	-	A	-	-	-	-	-	-	-	-	-	80	26					
7	Venkatesh	41	M	D.L	H.S.	-	A	-	+	-	-	-	-	-	+	-	-		N		LCI		Cerebellar Syndrome
8	Neethu	38	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	-	285	28					
9	Ponamma	25	F	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	366	28					
10	Vijayakumar	32	M	DRV	H.S.	-	B	-	+	+	-	-	-	-	-	-	-	-	P		MCAI		CVA
11	Arun Kumar	29	M	DRV	H.S.	-	A	-	-	-	-	-	-	-	-	-	261	27					
12	Manimozhi	50	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	171	26					
13	Natranajan	35	M	BSN	H.S.	-	A	-	-	-	-	-	-	-	-	-	136	26					
14	Edukondalu	21	M	D.L	H.S.	TBA	A	-	+	-	+	-	-	-	-	-	124	-	N	EP , PL	N		TB Meningitis
15	Rajeshwari	32	F	H.W	H.S.	-	W	+	-	-	-	-	-	-	-	-	289	27	P	N	MCG		Multiple Granoloma
16	Vijay	33	M	P	H.S.	-	W	-	-	-	-	-	-	-	-	-	177	26					
17	Dilip	40	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	346	27					
18	Murugesh	38	M	AGR	H.S.	-	A	+	+	-	-	-	-	-	-	-	89		-	EP , PL	N		TB Meningitis
19	Jothi	25	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	-	200	28					
20	Zakir Hisian	35	M	DRV	H.S.	-	A	-	-	-	-	+	-	-	+	-	529	24	N		N	N-ms	Neurosyphilis
21	Ravi	45	M	P	H.S.	-	W	-	-	-	-	-	-	-	-	-	213	27					
22	Kumar	35	M	D.L	H.S.	-	A	-	-	-	-	-	+	-	-	-			-	N	N	NPH	ACUTE FLACCID PARALYSIS
23	Nethaji	38	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	65	26					
24	Lakshmipathi	33	M	D.L	H.S.	-	A	-	-	+	-	-	-	-	-	-	194	26	N		MCAI		CVA
25	Valiban	41	M	UE	H.S.	-	A	-	-	-	-	+	-	-	-	-	176	27	N	N		N-ms	HIV Myelopathy
26	Uyusufkhan	41	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	184	26					
27	Ravikumar	35	M	DRV	H.S.	-	A	-	-	-	-	-	-	-	-	-	253	27					
28	Vadivelu	32	M	D.L	H.S.	-	A	-	+	-	-	-	-	-	-	-	142	-	N	EP , PL	N		TB Meningitis
29	Venkatammal	40	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	-	178	28					
30	Chandrasekar	36	M	P	H.S.	-	B	+	+	-	-	-	-	-	-	-	94	-	P	EP , PL	N		TB Meningitis
31	Vediyappan	28	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	220	28					
32	Sumathi	20	F	H.W	H.S.	-	A	-	-	-	-	-	-	-	-	-	291	26					
33	Selvaraj	38	M	P	H.S.	-	W	-	-	-	-	-	-	-	-	-	286	27					
34	Muthuraman	56	M	D.L	H.S.	-	B	-	-	-	+	-	-	-	-	-	177	26	N	N	N		Seizure Disorder
35	Velarmathy	30	F	H.W	H.S.	-	W	-	-	-	-	-	-	+	-	-	365	27	N				Peripheral Neuropathy
36	Vivekannan	48	M	D.L	H.S.	-	A	+	+	-	-	-	-	-	-	-	125	-	P	EP , PL	N		TB Meningitis
37	Amudha	45	F	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	251	26					
38	Kumar	40	M	P	H.S.	-	A	-	-	-	-	-	-	-	-	-	257	25					
39	Suresh	35	M	MEC	H.S.	-	A	-	-	-	-	-	-	-	-	-	114	26					
40	Muthusamy	38	M	D.L	H.S.	-	A	+	-	-	-	-	-	-	-	-	136	24	N	EP , PL	N		TB Meningitis
41	Paranjothy	36	M	P	H.S.	-	W	-	-	+	-	-	-	-	-	-	206	26	N		MCAI		CVA
42	Kasthuri	30	F	D.L	H.S.	-	A	-	-	-	-	-	-	-	-	-	285	27					
43	Subharao	34	M	MEC	H.S.	-	W	-	-	-	-	-	-	-	-	-	206	27					
44	Jayaraj	48	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	-	253	26					
45	Ithayan	40	M	AGR	H.S.	-	A	-	-	-	-	-	-	-	-	-	204	25					
46	Rajalakshmi	29	F	H.W	H.S.	-	W	-	-	-	-	+	-	-	-	-	176	26	N	EP ,A			GBS

47	Ramesh	32	M	DRV	H.S.	-	W	-	-	-	-	-	-	-	-	236	27						
48	Sekar	27	M	DRV	H.S.	-	A	-	+	+	+	-	-	-	-	-		-	EP ,PL	N		TB Meningitis
49	Kesavan	43	M	MEC	H.S.	-	A	-	-	-	-	-	-	-	-	254	24	N				Myopathy
50	Alamelu	30	F	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	128	26					
51	Valli	27	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	161	27					
52	manickam	37	M	DRV	H.S.	-	W	-	-	-	-	-	-	-	-	513	28					
53	Suresh	28	M	P	H.S.	-	A	-	-	-	-	-	-	-	-	102	26					
54	Lakshmanan	36	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	173	27					
55	Fathima	24	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	192	28					
56	Balaiah	40	M	P	H.S.	-	W	-	-	-	-	-	-	+	-	410	28	N				Peripheral Neuropathy
57	Jayapal	43	M	DRV	H.S.	-	A	-	-	-	-	-	-	-	-	71	27					
58	Susmitha	23	F	ACC	H.S.	-	W	-	-	-	-	-	-	-	-	254	26					
59	Selvi	29	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	210	27					
60	Raja	40	M	DRV	H.S.	-	W	-	-	-	-	-	-	-	-	171	27					
61	Vijayan	37	M	UE	H.S.	-	A	-	+	-	+	-	-	-	-	-		-		N		MENINGOENCEPHALITIS
62	Ratchagan	35	M	DRV	H.S.	-	W	-	-	-	-	+	-	-	-	215	25	N	EP , A			GBS
63	Vadivelu	41	M	P	H.S.	-	W	-	-	-	-	-	-	-	-	111	27					
64	Murugan	57	M	BSN	H.S.	-	W	-	-	-	-	-	-	-	-	282	26					
65	Saraswathy	27	F	H.W	H.S.	-	A	-	-	-	-	-	-	-	-	210	28					
66	Ramana	32	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	193	27					
67	Baskar	31	M	D.L	H.S.	-	A	+	-	-	+	-	-	-	-	54	22	N	EP , PL	N		TB Meningitis
68	Murugeshan	42	M	P	H.S.	-	A	+	+	-	-	-	-	-	-	126	23	N	EP ,OL , I.I+	N		Crptococcal Meningitis
69	Rajendran	41	M	DRV	H.S.	-	W	-	-	-	-	-	-	-	-	134	27					
70	Abdul Hamaal	45	M	BSN	H.S.	-	W	-	-	-	-	-	-	-	-	101	26					
71	Meyyan	36	M	D.L	H.S.	-	A	-	-	-	-	-	-	-	-	241	27					
72	Dinesh	41	M	D.L	H.S.	-	A	+	+	-	-	-	-	-	-	116		P	EP , PN	N		Pyogenic Meningitis
73	Hemavathi	26	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	262	26					
74	Veerasamy	40	M	BSN	H.S.	-	W	-	-	-	-	-	-	-	-	98	27					
75	Thailammal	32	F	AGR	H.S.	-	A	-	-	-	-	-	-	-	-	126	28					
76	Kasinathan	45	M	UE	H.S.	-	B	+	-	-	+	-	-	-	-	186	26	N	EP ,PL	N	MRE	Tuberculoma
77	Louis	35	M	DRV	H.S.	-	A	-	-	-	-	-	-	-	-	339	27					
78	Amudha	36	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	1090	27					
79	Kumar	32	M	D.L	H.S.	-	W	+	+	-	-	-	-	-	-	210		N	EP,PL	N		TB Meningitis
80	Rangan	50	M	D.L	H.S.	-	A	-	-	-	-	-	-	-	-	77	26					
81	Ramesh	37	M	DRV	H.S.	-	A	-	-	-	-	-	-	-	-	182	27					
82	Jayaraman	32	M	P	H.S.	-	W	-	-	-	-	-	-	-	-	252	25					
83	Munusamy	35	M	AGR	H.S.	-	A	-	-	-	-	-	-	-	+	9	20	N		N	EWL	PML
84	Amsavel	34	M	AGR	H.S.	-	W	+	-	-	-	-	-	-	-	54	22	HR	N	N		AIDS Dementia Complex
85	Chandru	36	M	P	H.S.	-	W	-	-	-	-	-	-	-	-	325	26					
86	Raju	38	M	D.L	H.S.	-	A	-	-	-	-	-	-	-	-	250	27					
87	PeriyaSamy	42	M	AGR	H.S.	-	W	-	-	-	-	-	-	-	-	226	26					
88	Palani	32	M	D.L	H.S.	-	A	+	+	-	-	-	-	-	-	114		P	EP , PL	N		TB Meningitis
89	Deepa	28	F	P	H.S.	-	W	-	-	-	-	-	-	-	-	324	27					
90	Bashir	35	M	DRV	H.S.	-	A	-	-	-	-	-	-	-	-	189	26					
91	Rajammal	32	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	292	28					
92	Ilavarasi	34	F	AGR	H.S.	-	W	-	-	-	-	-	-	-	-	186	27					
93	Rajkumar	29	M	D.L	H.S.	-	W	-	-	-	-	-	-	-	-	326	26					

94	Ashok Kumar	36	M	MEC	H.S.	-	A	+	+	-	+	-	-	-	-	-	104		N	EP , PN	N		pyogenic meningitis
95	Gandhi Madhi	40	F	H.W	H.S.	-	W	-	-	-	-	-	-	-	-	-	224	27					
96	Suresh Kumar	23	M	DRV	H.S.	-	W	-	-	-	+	-	-	-	-	-	164	26	N	N	N		Seizure disorder
97	Vedaiya	34	M	P	H.S.	-	W	-	-	-	-	-	-	-	-	-	294	25					

OutCome
Expired
Expired
Expired
StatusQuo
Expired
Status Quo
Expired
Improved
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Improved
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Status Quo
Expired

Expired
Improved

F -	Female
M -	Male
AGR -	Agriculture
D.L	Daily Labourer
DRV -	Driver
H.W	House Wife
MEC -	Mechanic
P -	Painter
UE -	Unemployed
STU -	Student
BSN -	Business
ACC -	Accountant
H.S -	Heterosexual
I.V	Intravenous drug abuser
PTB	Pulmonary Tuberculosis
TBA -	Tuberculous adenitis
W -	Working
A -	Ambulatory
B -	Bedridden
H -	Headache
AS -	Altered Sensorium

Hem -	Hemiplegia
S -	Seizures
P -	Paraparesis
Q -	Quadriparesis
Pa	Paraesthesias
CS -	Cerebellar Syndrome
I.M	Involuntary Movements
MMSE -	Mini mental score examination
F -	Fundus
C.S.F -	Cerebrospinal fluid analysis
N -	Normal
P -	Pappilloedema
EP, PL -	Elevated proteins, Predominant lymphocytes
EP, A	Elevated proteins, acellular
EP, PN -	Elavated proteins, Predominant neutrophils
EP, OL, I.I-	Elevated proteins, Occational lymphocytes, India ink positive
MCAI -	Middle Cerebral arterial territory infarct
MCG -	Multiple calcified granuloma
EWL -	Extensive White Matter lesions
MRE -	Multiple Ring enhancing lesions
NPH -	Normal pressure hydrocephalus
N-ms	Normal MRI spine